

1,1,1,3,3,3-Hexamethyldisilazane (2018)

I. IDENTIFICATION (ECHA, 2017; NTP, 1991; OECD, 2009a, 2009b)

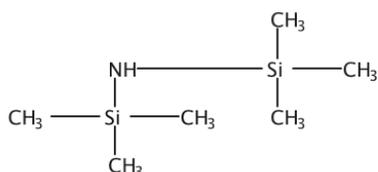
Chemical Name: 1,1,1,3,3,3-Hexamethyldisilazane

Synonyms: Hexamethyldisilazane; HMDZ

CAS Number: 999-97-3

Molecular Formula: C₆H₁₉NSi₂

Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES (ECHA, 2017; NTP, 1991; OECD, 2009a, 2009b)

Molecular Weight: 161.4 g/mol

Physical State and Appearance: Colorless liquid with an ammonia odor

Conversion Factors: Not available

Melting Point: -76.2 ± 1.9 °C (-105.16 °F ± 35.42 °F)

Boiling Point: 125 °C (258.8 °F) at 1013 hPa

Flammability Limits: 0.3 - 41% in air (extremely sensitive to electric discharge). Highly flammable.

Flash Point: 27 °C (81 °F) [closed cup]; 11 °C at 101.3 kPa

Autoignition Temperature: 325 °C at 1013 hPa

Specific Density: ~ 0.7741 g/cm³ at 25 °C (77 °F)

Vapor Pressure: 22 hPa at 25 °C (~100,000 ppm)

Vapor Density: No data available

Log K_{ow}: 2.62 (calculated)

Water Solubility: ~761 mg/L at 25 °C (77 °F)

Other Solubility: No data available

Stability: HMDZ undergoes rapid hydrolysis in the presence of water and is expected to form ammonia and trimethylsilanol. The t_{1/2} @ pH 4 ≤ 2.5 seconds at 1.5 °C; t_{1/2} @ pH 7 ≤ 28.5 seconds at 1.5 °C; and t_{1/2} @ pH 9 ≤ 6.0 seconds at 1.5 °C.

III. USES (ECHA, 2017; NTP, 1991; OECD, 2009a, 2009b)

HMDZ is used industrially to treat the surface of silica; as an intermediate as an adhesion promoter or silylating agent (to form silicon-containing groups (R₃Si)) in the semiconductor industry; as a chemical modifier of inorganic fillers; and as a water scavenger in some silicone sealants. HMDZ is also used for deactivating glass wool and treating GC injection port glass inserts. HMDZ is a universal silylating agent used for deriving alcohols, carboxylic acids, amines, amides, mercaptans, and other compounds. HMDZ is a common choice for silylation of sugars and related substances. HMDZ is a selective protective group reagent in organic synthesis.

HMDZ is added to silicone home maintenance sealants at 1-5% as a scavenger for any free water or methanol that may be present, which extends the shelf life of the product.

IV. ANIMAL TOXICITY DATA

A. Acute Toxicity and Irritancy

1. Lethality Data (ECHA, 2017; NTP, 1991; OECD, 2009a, 2009b)

Species, Route	LD ₅₀ or LC ₅₀
Rat, Oral	813 mg/kg
Rat, Oral	774 mg/kg
Rat, Oral	1.1 ml/kg (851 mg/kg) [95% CI = 1.0 – 1.2 ml/kg]
Rabbit (male), Skin	0.761 ml/kg (859 mg/kg) [24-hour occluded]
Rabbit (female), Skin	0.707 ml/kg (547 mg/kg) [24-hour occluded]
Rat, Inhalation, 1 hr	> 1016 ppm (> 6.7 mg/L)
Rat, Inhalation, 4 hr	1561 ppm (10.3 mg/L)
Rat, Inhalation, 6 hr	1516 ppm (10 mg/L) [95% CI = 1198–1920 ppm]
Rat, Inhalation, 4 hr [calculated from the 6-hr LC ₅₀]	1857 ppm (12.2 mg/L)

2. Eye Irritation

In this study, undiluted HMDZ (0.1 ml) was instilled into the eyes of male, New Zealand White rabbits (n=3) as per OECD 405. (OECD, 2009a, 2009b) A very slight, immediate pain response was observed in all animals. The test material caused slight conjunctival hyperemia in two animals and slight conjunctival chemosis in one animal at the 1 hour reading; these reactions had subsided by subsequent readings (2 or 24 hours). The primary eye irritation score (PII) was 0/110 (non-irritating).

Undiluted HMDZ (0.1 ml) was instilled into the eyes of male or female, New Zealand White rabbits (n=6) as per OECD 405. (OECD, 2009a, 2009b). Only trace iritis was seen in one eye at 1-hour and trace conjunctival irritation (redness and/or discharge) was seen in 4/6 eyes. No irritation was evident at 24 hours.

Undiluted HMDZ (0.1 ml) was instilled into the eyes of New Zealand White rabbits (n = 5) in a study consistent with OECD 405 (OECD, 2009a, 2009b). No conjunctival, iridial, or corneal irritation was observed. All scores at all scoring intervals were recorded as 0 (PII = 0/110).

3. Skin Absorption

Based on the results of the dermal lethality studies in male and female rabbits (see above), HMDZ is capable of being dermally absorbed in potentially toxic amounts.

4. Skin Irritation

In this study, 0.5 ml Dow Corning® Z-6079 (100% w/w HMDZ) was applied for 4 hours under semi-occlusion, to the shaved skin of male, New Zealand White rabbits (n=3) as per OECD 404 (Dow Corning Corporation, 1993). After washing, dermal irritation was scored at 1, 24, 48, 72 hours and 7 days for erythema, edema and other evidence of irritation or injury. No irritation was observed at the 1-hour reading. Erythema was observed at 24, 48 and 72 hours in two rabbits. All signs of irritation had subsided by day 7. The third animal showed no signs of irritation during the study. The primary dermal irritation score (PII) was calculated to be 1.22/8.0 (minimally irritating).

In another study, 0.5 ml of HMDZ was applied to the shaved skin of six New Zealand White rabbits for 4 hours as per OECD 404 (ECHA, 2017; NTP, 1991; OECD, 2009a, 2009b). Sites were scored (Draize) at one hour, and at 1, 2, 3 and 7 days post-exposure. Moderate edema was observed in one rabbit at day 7. The other five rabbits had no erythema or edema, but necrosis was observed under the adhesive tape and under the

restraining rods. Note: The observed necrosis was very likely due to the HMDZ being trapped, in direct contact with the skin, under occlusive conditions (the observation of dermal necrosis in this study is in direct contrast to what was observed when HMDZ, as Dow Corning® Z-6079, was held in place with a semi-occlusive dressing, as called for in OECD 404 methodology).

In another acute dermal irritation study using a protocol that was comparable to OECD 404, HMDZ (0.5 ml) was applied to the shaved skin of six New Zealand white rabbits under an occlusive (impervious) dressing for four hours. [1,2] Skin reactions were scored (Draize) at one hour, 1, 2, 3, 7, 10 and 14 days post-exposure. Exposure resulted in severe erythema, moderate to severe edema and necrosis of the skin of 6/6 rabbits. Ecchymosis developed in five rabbits. After two days, scabs were apparent at the exposure sites. One rabbit had ulceration at seven days, which persisted to day 14 post-exposure. Scabs and desquamation were evident on each rabbit after 14 days. Note: The observed necrosis, etc. was very likely due to the HMDZ being trapped, in direct contact with the skin, under occlusive conditions. (Again, these observations are in direct contrast to what was observed when HMDZ, as Dow Corning® Z-6079, was held in place with a semi-occlusive dressing, as called for in OECD 404 methodology).

5. Skin Sensitization

No data available.

6. Inhalation Toxicity

In an acute inhalation lethality (LC₅₀) study, male and female SD rats (5/sex) were exposed via whole-body exposure, as per OECD 403, to HMDZ vapor at 1016 ppm (6.7 mg/L) for one hour (ECHA, 2017; NTP, 1991; OECD, 2009a, 2009b). There was no mortality. Clinical signs of toxicity were observed only during exposure and included hypoactivity and respiratory difficulties (noted as abdominal breathing). No clinical signs of toxicity were observed following exposure, and no signs of toxicity were observed following exposure or during the 14-day post-exposure period. Increases in mean body weight gains (no data provided) were observed for both sexes on post-exposure days 7 and 14. No macroscopic lesions were observed in any of the animals. The 1-hour LC₅₀ was determined to be > 1016 ppm (> 6.7 mg/L).

In an acute inhalation lethality (LC₅₀) study, male and female SD rats (2/sex/dose) were exposed to HMDZ vapor at 5.6, 19.0, 30.4, 60.5, or 94.3 mg/L for four hours. (ECHA, 2017; NTP, 1991; OECD, 2009a, 2009b) There was 100% mortality at

concentrations ≥ 19.0 mg/L and no mortality at 5.6 mg/L. The following were noted in the 5.6 mg/L exposure group: hypoactivity after 10 minutes of exposure, ataxia and dyspnea were observed at the three-hour time point, and ataxia and loss of righting reflex within one hour after exposure (persisted for approximately 18 hours). The 4-hour LC_{50} was determined to be 1561 ppm (10.3 mg/L).

In an acute inhalation lethality (LC_{50}) study, male and female SD rats (5/sex per dose) were exposed via whole-body exposure, as per OECD 403, to HMDZ at concentrations of 900, 1200 and 3450 ppm (5.9, 7.8 and 22.6 mg/L) for six hours. (Dow Corning Corporation, 2007a) Deaths were reported in 0/5, 3/5 and 5/5 males and in 0/5, 2/5 and 5/5 females exposed at 5.9, 7.8 and 22.6 mg/L, respectively. At 5.9 mg/L, all animals were inactive and exhibited lacrimation, partially-closed eye lids, coldness when touched, soft/limp muscles, slow/noisy respiration and soiling (around eyes or urogenital area). Most animals returned to normal by day 3 or 4; however, one female had decreased/no activity and eye/urogenital soiling until day 5. Clinical observations noted in all animals at 7.8 mg/L were similar to those at 5.9 mg/L, but also included lethargy and labored respiration. In the animals that recovered and went on to the scheduled terminal sacrifice, these observations typically persisted until days 3 or 4, returning to normal by day 5. Body weight gains at 5.9 mg/L averaged approximately 12%, while those for the surviving animals in the 7.8 mg/L group averaged approximately -1% over the 15-day observation period. The 6-hour LC_{50} determined to be 1516 ppm (10 mg/L). [The calculated 4-hour LC_{50} from this 6-hour LC_{50} was determined to be 1857 ppm (12.2 mg/L)].

While no studies have been performed to determine the potential for respiratory tract irritation, it can be surmised that HMDZ may be a respiratory tract irritant based on clinical observations noted during the acute inhalation studies. These observations included: slow/noisy respiration, labored respiration, and respiratory difficulties (abdominal breathing).

Lastly, observations of both decreased activity and ataxia during acute exposure to high concentrations of HMDZ indicate that HMDZ can also cause CNS depression under certain exposure conditions.

B. Subacute Toxicity

1. Inhalation

Male and female SD rats (5/sex per exposure group) were exposed to HMDZ measured vapor concentrations of 0 (control), 31 ppm (± 0.5), 107 ppm (± 1.7), 306 ppm (± 1.0),

and 584 ppm (± 4.2), via whole-body inhalation, for 6 hours/day, for 7 consecutive days, based OECD Guideline 412. (Dow Corning Corporation, 2007b) This range-finder study was performed to determine exposure concentrations for longer-term studies.

There were no deaths prior to the scheduled necropsy or no gross pathologic observations (abdominal, cranial, oral or thoracic cavities) in any of the exposed animals.

The following were noted at 584 ppm: 1) Either decreased or no activity accompanied by either the inability to walk or severe, uncoordinated gait during exposure; these effects were, however, transient and the animals were observed to recover prior to the next day's exposure; 2) A statistically significant reduction in both mean body weight and mean body weight gain over the exposure period; and 3) A statistically significant reduction in food consumption in males and females.

The following were noted at 306 ppm: 1) Decreased activity and slight uncoordinated gait in a few animals; 2) A reduction in both mean body weight and mean body weight gain over the exposure period; and 3) A statistically significant reduction in food consumption in only females.

None of the observations on activity, body weight, body weight gain or food consumption were noted in either the 107 or 31 ppm exposure groups. Therefore, the study NOAEL is considered to be 107 ppm.

The potential toxicity of HMDZ was assessed as part of a combined repeated-dose inhalation toxicity study that included reproductive/developmental toxicity screening as per OECD 422. [2,8] In the toxicity portion of this study, HMDZ was administered to groups of male (10/group) and female (10/group) SD rats via whole-body vapor inhalation for six hours/day, seven days/week to target concentrations of 0 (filtered air), 25, 100 and 400 ppm (0.16, 0.66, and 2.66 mg/L). Males and females were exposed to HMDZ vapor for a total of 29 and 28 days, respectively.

The following were noted at 400 ppm: 1) A significant increase in the incidence of decreased behavior/activity and uncoordinated gait in both males and females (by initiation of the next day's exposures, these observations had subsided); 2) Statistically-significant decreases in both absolute body weights for only females (15%) and total weight gain for both males and females (62 and 25%, respectively); 3) Statistically-significant decreases in average daily food consumption for males and females during week one and in total food consumption for both sexes; 4) Statistically-significant decreases in glucose (males

only) and increases in cholesterol in both males and females; 5) A slight, statistically-significant decrease in absolute epididymides weight and a statistically-significant increase in relative kidney weight in males; 6) A slight, statistically-significant decrease in absolute brain and lung weights in females and a statistically-significant increase (relative to body weight) in brain, kidney and liver weights in females; and 7) a statistically-significant increased incidence of hepatocellular hypertrophy in females (note: there were no associated increases in any hepatic enzyme parameters such as ALT, AST, ALP, etc.).

The following were noted at 100 ppm: 1) A statistically-significant decrease in day-29 absolute body weight in females (however, total weight gain and percent weight gain were not statistically significantly different); and 2) A statistically-significant increase in relative kidney weight in females.

The following were noted at 25 ppm: No exposure-related findings on any parameter evaluated.

Lastly, all animals survived to scheduled necropsy; there were no exposure-related effects on neurobiological function (as evaluated by Functional Observational Battery and motor activity evaluations); there were no exposure-related effects on hematological parameters (including prothrombin times); and there were no gross pathological observations associated with HMDZ exposure.

The study report concluded that the systemic toxicity NOAEL was 100 ppm, and the LOAEL was 400 ppm.

2. Oral

No data are available.

C. Subchronic Toxicity

1. Inhalation

In a GLP-compliant, 90-day inhalation study done in accordance with OECD 413, four groups of male and female Sprague-Dawley rats (10/sex per group) were exposed by nose-only inhalation to target vapor concentrations of 0 (control; filtered air), 25, 75 and 400 ppm (0.0, 0.17, 0.50 and 2.67 mg/L air) HMDZ for 6 hours per day, 5 days/week for 13 weeks. (Harlan Laboratories, 2014) In this main study, all animals received at least 65 exposures at approximately 24-hour intervals. In addition to the main study, four groups of male and female SD rats (10/sex per group) were also exposed, nose-only, to 0 ppm (control; filtered air) and 400 ppm HMDZ vapor for assessment followed by a 4-week recovery period.

There were no unscheduled deaths, no ophthalmic findings, or exposure-related macroscopic (gross pathologic) findings in any animals, at any of the three HMDZ exposure concentrations.

Exposure to 25 or 75 ppm HMDZ was not associated with any effects, with the exception of what was noted for the male kidneys (see below).

The following were noted at 400 ppm: 1) Ataxia and decreased activity was noted in all animals after exposure from the first day of treatment onwards. [In general, these clinical signs had receded on the following day]; 2) A slight, but statistically significantly reduced food intake was noted in both sexes during the first two weeks of treatment [After the end of treatment food intake increased, indicating recovery]; 3) A statistically significant decrease in body weight gain in males during the first 4 weeks of treatment and in females generally during the first month and last two weeks of treatment; 4) A statistically significant increase in total RBC and hematocrit at the end of the treatment period in females [However, all values were still within the range of historical control data and at the end of the recovery period the values were similar to controls]; 5) Sodium, potassium and chloride levels were slightly, but statistically significantly increased at the end of the treatment period in females. Total protein was also slightly reduced for those animals. [However, all values were still within the range of historical control data. At the end of the recovery period the values for sodium and chloride were similar to controls]; 6) A slight, but statistically significant decrease in urine pH at the end of the treatment period in males. [However, the value was still within the range of historical control data and at the end of the recovery period the values were similar to controls]; and 7) A statistically-significant increase in liver:body weight ratio in females. [No difference was noted after recovery period].

Changes considered to be associated with HMDZ exposure were present in the kidneys of males from all the treated groups. In comparison to controls the incidence and severity of increased intra-epithelial hyaline droplets and focal or multifocal basophilic tubules was greater in all the treated male groups. The increase was dose-dependent for intra-epithelial hyaline droplets, but tubular basophilia did not show a clear dose-dependency. Granular casts were present at the corticomedullary junction of the kidneys in 2/10 males in the 400 ppm exposure group. These observations are consistent with the diagnosis of alpha 2u-nephropathy in the male rats. After a four-week post-exposure recovery period, no treatment-related changes were present, indicating complete reversal of the renal findings observed in the male rats.

The 90-day inhalation study NOAEL was determined to be 75 ppm. With regards to the kidney observations noted in only the male rats, these are entirely consistent with the diagnosis of alpha-2u-nephropathy (Doi et al., 2007; Flamm and Lehman-McKeeman, 1991; Swenberg, 1993; US EPA, 1991). With regards to the development of a health-based WEEL, the diagnosis of male rat-specific alpha-2u-nephropathy is not considered to be either suitable or relevant for extrapolation to human health risk assessment.

2. Oral

No data are available.

D. Chronic Toxicity/Carcinogenicity

No data are available.

E. Reproductive/Developmental Toxicity

In a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening Test (OECD 422), HMDZ vapor was administered via whole-body inhalation for six hours/day, seven days/week to male and female SD rats at target concentrations of 0, 25, 100 and 400 ppm (0.16, 0.66, and 2.66 mg/L). (Dow Corning Corporation, 2008) Male rats were exposed for 14 days pre-mating and during mating for up to a total of 28 days; female rats were exposed during pre-mating (14 days) and mating, up to and including day 19 of gestation, and then up to and including postpartum 3 up to a total of 42 days.

The dams and pups were observed daily during the lactation period for survival and behavioral abnormalities in nursing. Developmental parameters evaluated included presence of external abnormalities, mean litter size, offspring survival, sex ratio, and offspring body weight gain. Dams and pups were euthanized on postpartum day 4 and examined for external gross lesions. Macroscopic examination was performed at necropsy for the pups. No tissues were collected from the dams or pups for microscopic examination. There were no HMDZ treatment-related effects on any of the developmental parameters assessed.

There was no exposure-related effects on female reproductive performance. There were no HMDZ exposure-related effects on any reproductive parameter endpoint assessed (mean gestation length, mean litter size, mean live litter size, mean litter weight, mean pup weight, day 4 viable pups, mean ratio of live births:litter size, mean number of implantation sites, mean number of corpora lutea, and mean mating and fertility indices).

The NOAEL for reproductive and developmental toxicity was established at 400 ppm.

F. Genotoxicity/Mutagenicity

1. *In vitro*

In GLP-compliant assays for gene mutation in bacteria (OECD 471), HMDZ was negative, both with and without metabolic activation (\pm S9), in *S. Typhimurium* strains TA98, 100, 1535, 1537 and 102 and in *E. coli* WP2uvrA

In GLP-compliant assays for gene mutation in mammalian cells (OECD 476), HMDZ was negative, both with and without metabolic activation (\pm S9), in mouse lymphoma L5178Y cells.

In GLP-compliant assays for chromosomal abnormalities in mammalian cells (OECD 473), HMDZ did not induce chromosomal aberrations, either with or without metabolic activation (\pm S9), in human peripheral blood lymphocytes.

In another assay for chromosomal abnormalities in mammalian cells (comparable to OECD 473), HMDZ did not induce chromosomal aberrations in Chinese Hamster Ovary (CHO) cells, either with or without metabolic activation (\pm S9).

2. *In vivo*

No data available.

G. Metabolism/Pharmacokinetics

No data are available.

V. HUMAN USE AND EXPERIENCE

No published studies examining exposure levels or health effects experienced in workers handling HMDZ were identified.

VI. RATIONALE

1,1,1,3,3,3-Hexamethyldisilazane (HMDZ) is considered to be slightly, to at most, moderately toxic following acute administration via the oral, dermal and inhalation routes of exposure. HMDZ was not dermally irritating to rabbits in a well-conducted study; however, it was shown to cause dermal necrosis, in other studies, under occlusive conditions. HMDZ is not an eye irritant. HMDZ is not genotoxic/mutagenic in *in vitro* assays. Short-term, high dose inhalation exposure to HMDZ produced both respiratory tract irritation and reversible CNS depression. HMDZ did not cause either reproductive or developmental toxicity in rats. In subacute inhalation studies, effects noted following high-dose HMDZ exposure included

decreased activity, reduced food consumption, changes in clinical chemistry parameters, and hepatocellular hypertrophy (only in females and with no associated histopathology and/or changes in hepatic enzyme parameters). In a 90-day inhalation study, many of the same effects seen in the subacute studies were also noted and were determined to be either non-adverse or adaptive responses to HMDZ exposure. Lastly, in the 90-day study, HMDZ exposure-related effects were observed in the kidneys of male rats. However, after a four-week post-exposure recovery period, none of the exposure-related kidney changes were present. Based on an assessment of these male-only kidney observations, it was conclusively determined that they were entirely consistent with the diagnosis of alpha-2u-nephropathy.

Based on the results of the 90-day inhalation study with HMDZ (Harlan Laboratories, 2014), 75 ppm was determined to be the definitive No Observed Adverse Effect Concentration (NOAEL) and was selected as the point of departure (PoD) for the derivation of the 8-hour TWA, health-based WEEL value. This subchronic inhalation NOAEL was adjusted to account for duration of exposure, inter-individual variability and intra-individual variability. The resulting 8-hour TWA WEEL value of 10 ppm is fully expected to provide a significant margin of safety against the production of any potential adverse health effects in workers following long-term inhalation exposure to HMDZ vapor.

In addition to establishing an 8-hour TWA WEEL, a Short-Term Exposure Limit (STEL) is also established to protect workers from reversible effects produced by acute, high-dose inhalation of HMDZ vapor. Specifically, decreased activity, ataxia, slow/noisy respiration, labored respiration, and respiratory difficulties (abdominal breathing) have been noted during acute exposure to high concentrations of HMDZ. These observations indicate that HMDZ may have the potential to cause CNS depression and respiratory tract irritation under acute, high-dose inhalation exposure conditions. Starting with PoDs ranging from 5.6 to 6.7 mg/L (850 – 1016 ppm) from the acute inhalation studies, and adjusting for duration of exposure, inter- and intra-individual variability, and effect(s) produced, a 15-minute STEL of 50 ppm was calculated.

Because of the experimentally-determined potential of HMDZ to be dermally absorbed in toxicologically-significant amounts, a skin notation (Skin) is also warranted for HMDZ.

VII. RECOMMENDED WEEL GUIDE

8-Hour Time-Weighted Average (TWA): 10 ppm

15-minute STEL = 50 ppm

Notation: Skin

VII. REFERENCES

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